



US006211368B1

(12) **United States Patent**  
Cooper et al.

(10) **Patent No.:** US 6,211,368 B1  
(45) **Date of Patent:** Apr. 3, 2001

(54) **PYRROLO(3,4-D)PYRIMIDINONE DERIVATIVES AND THEIR USE AS MEDICAMENTS**

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(\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/505,862**

(22) Filed: **Feb. 17, 2000**

**Related U.S. Application Data**

(63) Continuation of application No. 09/011,780, filed as application No. PCT/SE97/02157 on Dec. 18, 1997, now Pat. No. 6,046,204.

(30) **Foreign Application Priority Data**

Dec. 21, 1996 (GB) ..... 9626643

(51) **Int. Cl.<sup>7</sup>** ..... **C07D 487/04; A61P 27/00**

(52) **U.S. Cl.** ..... **544/280**

(58) **Field of Search** ..... 544/280

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69/17610 6/1996 (WO).

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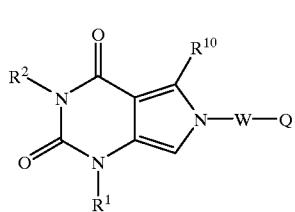
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(57)

**ABSTRACT**

Process for preparing 5-substituted pyrrolo [3,4-d] pyrimidine-2-4-diones of formula (I)



wherein W, Q, R<sup>1</sup>, R<sup>2</sup> and R<sup>10</sup> are as defined in the specification and Y is COOH, wherein a corresponding C<sub>1-5</sub> alkyl ester compound is hydrolyzed. The compounds are useful for treating or reducing the risk of reversible obstructive airways disease.

**1 Claim, No Drawings**

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**PYRROLO[3,4-D]PYRIMIDINONE  
DERIVATIVES AND THEIR USE AS  
MEDICAMENTS**

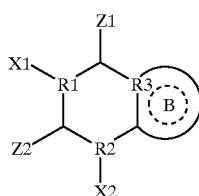
This application is a continuation of application Ser. No. 09/011,780, filed Feb. 24, 1998, now U.S. Pat. No. 6,046,204, which is a National Stage of application of PCT/SE97/02157, filed Dec. 18, 1997, which claims priority from British priority patent application Serial No. 9626643.2, filed Dec. 21, 1996.

The present invention provides certain novel 5-substituted pyrrolo[3,4-d]pyrimidine-2,4-diones, processes for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and methods of treatment involving their use.

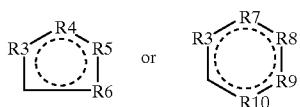
T-cells play an important role in the immune response, however in autoimmune disease T-cells are activated against particular tissues, e.g. causing the inflammation associated with rheumatoid arthritis. Interleukin-2 (IL-2) is an essential autocrine growth factor for T-cells and hence inhibition of IL-2 transcription is beneficial in the modulation of autoimmune disease. Formation of a transcriptional complex of the protein nuclear factor of activated T-cells-1 (NFAT-1) on the IL-2 promoter is essential for IL-2 transcription. NFAT-1 mediated transcription has therefore been proposed as appropriate molecular target for immunomodulation, Y. Baine et al., *J. Immunol.*, 1995, 154, 3667-3677.

W. F. Michne et al., in *J. Med. Chem.* (1995) 38, 2557-2569 disclose a number of quinazoline-2,4-diones and pyrrolo[3,4-d]pyrimidine-2,4-diones which inhibit transcription regulated by the DNA region bound by the NFAT-1 protein.

WO 96/17610 discloses the use of compounds of the following general formula and their salts as anti-ischaemic agents,



wherein R1, R2 and R3 which may be the same or different are N or CH; X1 and X2 which may be the same or different are hydrogen, hydroxy or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclyl group and Z1 and Z2 which may be the same or different are hydrogen, hydroxy, keto or an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclyl group or one of Z1 and X1 and Z2 and X2 form the second bond of a double bond at the 1,6 or 2,3 positions, with the proviso that at least one of the groupings R1Z1X1, R2Z2X2 and R1X1Z2 form a hydroxamate moiety ( $-\text{N}(\text{OH})\text{C}(=\text{O})-$ ) in which R1 and/or R2 is N, Z1 and/or Z2 is  $=\text{O}$  and X1 and/or X2 is OH or R1 is N, Z2 is  $=\text{O}$  and X1 is OH and B is a 5- or 6-membered ring of formula

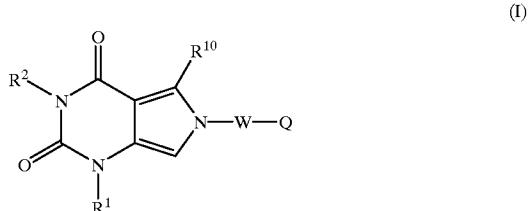


in which R4, R5, R6, R7, R8, R9 and R10 which may be the same or different are CH or N with the proviso that ring B

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cannot contain more than 3 ring members which are nitrogen and the ring B may optionally be substituted by one or more of hydroxy, keto and an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclyl group. Preferred compounds of WO 96/17610 include those compounds in which the ring B contains no substituent groups.

In accordance with the present invention, there is provided a compound according to the general formula:



wherein

20 W represents  $-\text{CH}_2-$  or a bond; Q represents  $\text{Ar}^1$  or  $\text{Ar}^2$ ; in the case where W represents  $-\text{CH}_2-$ , Q represents an aryl group  $\text{Ar}^1$  wherein  $\text{Ar}^1$  represents naphthyl, phenyl, quinolyl, isoquinolyl, indolyl, benzofuranyl or benzothienyl; in the case where W represents a bond, Q represents an aryl group  $\text{Ar}^2$  wherein  $\text{Ar}^2$  represents acenaphthényl, fluorenyl or indanyl; wherein the ring systems which  $\text{Ar}^1$  and  $\text{Ar}^2$  represent may all be optionally substituted by one or more substituents selected from  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy, halogen, or trifluoromethyl;  $R^{10}$  represents  $\text{X}-(\text{A})_p-\text{Y}$ ; X represents  $\text{S}(\text{O})_n$ ,  $\text{C}\equiv\text{C}$ ,  $(\text{CH}_2)_2$ ,  $\text{CH}=\text{CH}$  or  $\text{CH}_2\text{CH}=\text{CH}$ ; n represents 0, 1 or 2; A represents  $\text{C}_{1-6}$  alkylene; p is 0 or 1; Y represents  $\text{CN}$ ,  $\text{OR}^{11}$ ,  $\text{CO}_2\text{R}^{12}$ ,  $\text{CONR}^{13}\text{R}^{14}$ ,  $\text{NR}^{15}\text{R}^{16}$ ,  $\text{NHSO}_2\text{R}^{17}$ ,  $\text{NHCOR}^{18}$  or an optionally substituted aryl or heteroaryl group, provided that when X represents  $\text{S}(\text{O})_n$  and Y is other than an optionally substituted aryl or heteroaryl group, then p is 1 and also provided that when X represents  $\text{S}(\text{O})_n$ , p is 1 and Y represents OH, then n is not 0;  $R^{13}$  and  $R^{14}$  independently represent H,  $\text{C}_{1-5}$  alkyl or phenyl, which latter group may be substituted by one or 25 more substituents selected from  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy, halogen, or  $\text{CO}_2\text{R}^{21}$ ; and  $R^1$ ,  $R^2$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$  and  $R^{21}$  independently represent H or  $\text{C}_{1-5}$  alkyl; or a 30 pharmaceutically acceptable derivative thereof.

In the present specification, unless otherwise indicated, an 45 alkyl substituent or alkyl moiety in an alkoxy, alkoxy carbonyl, alkylsulphonamido, (di)alkylamido, (di)alkylamino or acylamino substituent group may be linear or branched.

When W in formula (I) represents  $-\text{CH}_2-$ , then Q 50 represents an aryl group  $\text{Ar}^1$  wherein  $\text{Ar}^1$  preferably represents a naphthyl or phenyl group, especially a naphthyl group, which aryl group may be optionally substituted by one or more, preferably one to four, particularly one or two, substituents selected from  $\text{C}_{1-4}$  alkyl, e.g., methyl or ethyl,  $\text{C}_{1-4}$  alkoxy, e.g. methoxy or ethoxy, halogen, e.g. fluorine, chlorine or bromine, or trifluoromethyl.  $\text{Ar}^1$  is preferably an 55 unsubstituted naphthyl group.

When W in formula (I) represents a bond, then Q represents an aryl group  $\text{Ar}^2$  wherein  $\text{Ar}^2$  preferably represents an 60 indanyl group, which may be optionally substituted by one or more, preferably one to four, particularly one or two, substituents selected from  $\text{C}_{1-4}$  alkyl, e.g. methyl or ethyl,  $\text{C}_{1-4}$  alkoxy, e.g. methoxy or ethoxy, halogen, e.g. fluorine, chlorine or bromine, or trifluoromethyl.  $\text{Ar}^2$  is preferably an 65 unsubstituted indanyl group.

Preferably, X represents  $\text{S}(\text{O})_n$  wherein n is 0, 1 or 2,  $\text{C}\equiv\text{C}$ ,  $(\text{CH}_2)_2$  or  $\text{CH}_2\text{CH}=\text{CH}$ . Particularly advantageous

compounds of formula (I) are those in which X represents  $S(O)_n$  wherein n is 0, 1 or 2.

When p is 1, A preferably represents  $C_{1-4}$  alkylene, more preferably  $CH_2$ ,  $(CH_2)_2$  or  $(CH_2)_3$ .

Each of groups  $R^1$ ,  $R^2$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$ ,  $R^{18}$  and  $R^{21}$  preferably represents H or a  $C_{1-4}$  alkyl group.  $R^1$  is most preferably a cyclic or branched  $C_{3-4}$  alkyl group, e.g., a 1-methylethyl or 2-methylpropyl group, and  $R^2$  is most preferably a methyl group.

Each of groups  $R^{13}$  and  $R^{14}$  preferably represents H,  $C_{1-3}$  alkyl or phenyl, which latter group may be substituted by one or more, e.g. one to four, substituents selected from  $C_{1-4}$  alkyl, e.g., methyl or ethyl,  $C_{1-4}$  alkoxy, e.g., methoxy or ethoxy, halogen, e.g. fluorine, chlorine or bromine, or  $CO_2R^{21}$ .

More preferably, each of groups  $R^{13}$  and  $R^{14}$  represents H,  $C_{1-3}$  alkyl or phenyl, which latter group may be substituted by one or two substituents selected from  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, halogen, or  $CO_2R^{21}$ .

Most preferably, each of groups  $R^{13}$  and  $R^{14}$  represents H,  $C_{1-3}$  alkyl or phenyl, especially H.

The group Y may represent an optionally substituted aryl or heteroaryl group. Preferably p is 0 when Y represents an optionally substituted aryl or heteroaryl group. Examples of aryl and heteroaryl groups include phenyl, furyl, imidazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, tetrazolyl and thieryl groups. The groups phenyl, 2-pyridyl, 4-pyridyl and 5-tetrazolyl are most preferred. Examples of substituents that may be present in the aryl or heteroaryl group include  $C_{1-4}$  alkyl, e.g. methyl or ethyl,  $C_{1-4}$  alkoxy, e.g. methoxy or ethoxy, halogen, e.g. fluorine, chlorine or bromine, hydroxyl and trifluoromethyl. One or more, e.g. 1, 2, 3 or 4, substituent groups may be present but preferably only one substituent group is present.

A preferred subset of compounds of formula (I) is one in which W represents  $-CH_2-$  or a bond; Q represents  $Ar^1$  or  $Ar^2$ ; in the case where W represents  $-CH_2-$ , Q represents an aryl group  $Ar^1$  wherein  $Ar^1$  represents naphthyl or phenyl; in the case where W represents a bond, Q represents an aryl group  $Ar^2$  wherein  $Ar^2$  represents indanyl; wherein the ring systems which  $Ar^1$  and  $Ar^2$  represent may all be optionally substituted by one or more, e.g. one, two, three or four, substituents selected from  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, halogen, or trifluoromethyl;  $R^{10}$  represents  $X-(A)_p-Y$ ; X represents  $S(O)_n$ ,  $C\equiv C$ ,  $(CH_2)_2$  or  $CH_2CH=CH$ ; n represents 0, 1 or 2; A represents  $C_{1-6}$  alkylene; p is 0 or 1; Y represents CN, OR<sup>11</sup>,  $CO_2R^{12}$ ,  $CONR^{13}R^{14}$ ,  $NR^{15}R^{16}$  or an optionally substituted phenyl, pyridyl or tetrazolyl group, provided that when X represents  $S(O)_n$  and Y is other than an optionally substituted aryl or heteroaryl group, then p is 1 and also provided that when X represents  $S(O)_n$ , p is 1 and Y represents OH, then n is not 0;  $R^{13}$  and  $R^{14}$  independently represent H,  $C_{1-5}$  alkyl or phenyl, which latter group may be substituted by one or more, e.g. one, two, three or four, substituents selected from  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, halogen, or  $CO_2R^{21}$ ; and  $R^1$ ,  $R^2$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{21}$  independently represent H or  $C_{1-5}$  alkyl.

An especially preferred subset of compounds of formula (I) is one in which W represents  $-CH_2-$  or a bond; Q represents  $Ar^1$  or  $Ar^2$ ; in the case where W represents  $-CH_2-$ , Q represents an aryl group  $Ar^1$  wherein  $Ar^1$  represents naphthyl; in the case where W represents a bond, Q represents an aryl group  $Ar^2$  wherein  $Ar^2$  represents indanyl;  $R^{10}$  represents  $X-(A)_p-Y$ ; X represents  $S(O)_n$ ,  $C\equiv C$ ,  $(CH_2)_2$  or  $CH_2CH=CH$ ; n represents 0, 1 or 2; A represents  $C_{1-3}$  alkylene; p is 0 or 1; Y represents CN, OR<sup>11</sup>,  $CO_2R^{12}$ ,  $CONR^{13}R^{14}$ ,  $NR^{15}R^{16}$  or a phenyl, pyridyl or

tetrazolyl group optionally substituted by a hydroxyl or methoxy group, provided that when X represents  $S(O)_n$  and Y is other than an optionally substituted aryl or heteroaryl group, then p is 1 and also provided that when X represents  $S(O)_n$ , p is 1 and Y represents OH, then n is not 0;  $R^{13}$  and  $R^{14}$  independently represent H; and  $R^1$ ,  $R^2$ ,  $R^{11}$ ,  $R^{12}$ ,  $R^{15}$  and  $R^{16}$  independently represent H or  $C_{1-4}$  alkyl.

Specific examples of preferred compounds of formula (I) are:

- (i) 5-[(3-hydroxypropyl)sulphiny1]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (ii) 5-[(3-hydroxypropyl)sulphonyl]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (iii) methyl 4-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoate;
- (iv) 5-[(3-methoxypropyl)thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (v) 5-[(2-hydroxyethyl)sulphiny1]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (vi) 4-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoic acid;
- (vii) 4-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoic acid, sodium salt;
- (viii) 5-[(2-dimethylaminoethyl)thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (ix) 6-(2,3-dihydro-1H-inden-2-yl)-5-[(3-hydroxypropyl)sulphiny1]-3-methyl-1-(1-methylethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (x) 6-(2,3-dihydro-1H-inden-2-yl)-5-[(3-hydroxypropyl)sulphonyl]-3-methyl-1-(1-methylethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (xi) 5-[(3-hydroxypropyl)sulphiny1]-3-methyl-1-(1-methylethyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (xii) 4-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanamide;
- (xiii) 5-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)pent-3-enoic acid;
- (xiv) 5-(5-hydroxypent-1-ynyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (xv) 5-(5-hydroxypentyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (xvi) 5-(4-hydroxybut-1-ynyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (xvii) 5-(4-hydroxybutyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;
- (xviii) 5-(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)pentanoic acid;
- (xix) 4-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanenitrile;
- (xx) 5-[(3-{1H-tetrazol-5-yl}propyl)thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;

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(xxi) 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-5-[(2-pyridinyl)thio]-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;

(xxii) 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-5-[(2-pyridinyl)sulphiny]-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;

(xxiii) 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-5-[(4-pyridinyl)thio]-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;

(xxiv) 5-([3-methoxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;

(xxv) 5-([3-hydroxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;

(xxvi) 5-([4-methoxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;

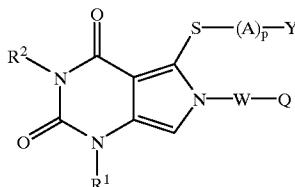
(xxvii) 5-([4-hydroxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione;

(xxviii) 5-([2-methoxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione; and

(xxix) 5-([2-hydroxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione.

According to the invention there is also provided a process for the preparation of a compound of formula I which comprises:

(a) when X represents  $S(O)_n$  and n is 1 or 2, oxidising a compound of general formula



(II)  
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wherein  $R^1$ ,  $R^2$ , A, p, Y, W and Q are as hereinbefore defined including the provisos, in the presence of an appropriate quantity of a suitable oxidising agent (e.g. 3-chloroperoxybenzoic acid or potassium peroxymonosulphate, commercially sold under the trade mark "OXONE") and an appropriate organic solvent (e.g. dichloromethane) under conditions which are well known to those skilled in the art;

(b) when Y represents  $OR^{11}$  and  $R^{11}$  represents  $C_{1-5}$  alkyl, reacting a corresponding compound of formula (I) in which Y represents OH, with an alkyl halide of general formula



wherein  $R^{11a}$  represents  $C_{1-5}$  alkyl and Hal represents a halogen atom such as bromine or iodine, for example, at 25° C. in the presence of a suitable base (e.g. sodium hydride) and a suitable organic solvent (e.g. tetrahydrofuran);

(c) when Y represents  $CO_2R^{12}$  and  $R^{12}$  represents  $C_{1-5}$  alkyl, esterifying a corresponding compound of formula (I) in which Y represents  $CO_2H$  with an alcohol of general formula



## 6

wherein  $R^{12a}$  represents  $C_{1-5}$  alkyl, under conditions that are well known to those skilled in the art;

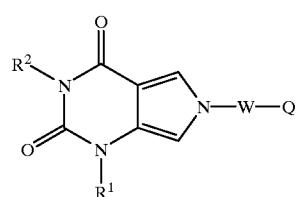
(d) when Y represents  $CONR^{13}R^{14}$ , reacting a corresponding compound of formula (I) in which Y represents  $CO_2H$  with an amine of general formula



wherein  $R^{13}$  and  $R^{14}$  are as hereinbefore defined, for example, at 25° C. in the presence of an appropriate peptide synthesis agent (e.g. diisopropylcarbodiimide and N,N-dimethylaminopyridine or, alternatively, ethyl chloroformate and triethylamine) and a suitable organic solvent (e.g. dichloromethane);

(e) when Y represents  $CO_2H$ , hydrolysing a corresponding compound of formula (I) in which Y represents  $CO_2R^{12}$  and  $R^{12}$  represents  $C_{1-5}$  alkyl, using a suitable base (e.g. lithium or sodium hydroxide) in a suitable solvent (e.g. aqueous tetrahydrofuran) at a temperature of from 0° C. to 80° C.;

(f) when X represents S, A represents a  $C_{1-6}$  alkylene group, Y represents  $CO_2R^{12}$  and  $R^{12}$  represents  $C_{1-5}$  alkyl, reacting a compound of general formula



(VI)

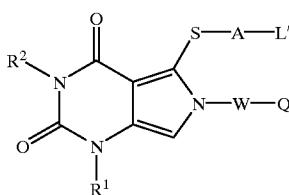
in which  $R^1$ ,  $R^2$ , W and Q are as hereinbefore defined, with a compound of general formula



wherein L is a suitable leaving group, for example para-toluenesulphinate, and A and  $R^{12}$  are as hereinbefore defined, in the presence of a suitable base, for example lithium diisopropylamide, in an appropriate solvent, for example tetrahydrofuran, at from -78° C. to room temperature, followed by hydrolysis of the resulting ortho ester;

(g) when X represents S, A represents a  $C_{2-6}$  alkylene group, Y represents  $NR^{15}R^{16}$  and  $R^{15}$  and  $R^{16}$  are as hereinbefore defined, reducing a corresponding compound of formula (II) as hereinbefore defined in which A represents a  $C_{1-5}$  alkylene group, Y represents  $CONR^{13}R^{14}$  and  $R^{13}$  and  $R^{14}$  are respectively equal to  $R^{15}$  and  $R^{16}$ , with a suitable reducing agent, for example diborane, in a suitable solvent, for example tetrahydrofuran;

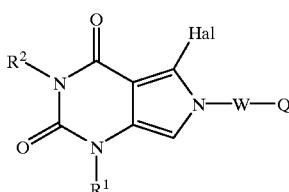
(h) when X represents S, A represents a  $C_{1-6}$  alkylene group, Y represents  $NR^{15}R^{16}$  and  $R^{15}$  and  $R^{16}$  are as hereinbefore defined, reacting a corresponding compound of general formula



(VIII)

wherein L' represents a leaving group such as paratoluenesulphonate and R<sup>1</sup>, R<sup>2</sup>, A, W and Q are as hereinbefore defined, with a compound of formula (V) wherein R<sup>13</sup> and R<sup>14</sup> are respectively equal to R<sup>15</sup> and R<sup>16</sup>, typically in a suitable solvent, such as dimethylformamide, in the presence of a suitable base, such as triethylamine;

j) when X represents C≡C, CH=CH or CH<sub>2</sub>CH=CH, reacting a compound of general formula



(IX)

in which Hal represents a halogen atom, e.g. bromine or iodine, and R<sup>1</sup>, R<sup>2</sup>, W and Q are as hereinbefore defined, with a compound of general formula (X), H—X'—(A)<sub>p</sub>—Y, in which X' represents C≡C, CH=CH or CH=CHCH<sub>2</sub> and A, p and Y are as hereinbefore defined in the presence of a palladium catalyst (e.g. bis-triphenylphosphinepalladium (II) chloride), and optionally hydrogenating the compound of formula (I) obtained wherein X represents C≡C or CH=CH in the presence of a palladium on carbon catalyst to produce a further compound of formula (I) wherein X represents (CH<sub>2</sub>)<sub>2</sub>;

(k) when X represents S, A represents a C<sub>1-6</sub> alkylene group and Y represents CN, reacting a compound of formula (VIII) as hereinbefore defined with sodium cyanide (NaCN);

(l) when X represents S, A represents a C<sub>1-6</sub> alkylene group and Y represents NH<sub>2</sub>R<sup>17</sup>, reacting a corresponding compound of formula (I) in which Y represents NH<sub>2</sub> with a compound of general formula (XI), R<sup>17</sup>SO<sub>2</sub>Cl, wherein R<sup>17</sup> is as hereinbefore defined;

(m) when X represents S, A represents a C<sub>1-6</sub> alkylene group and Y represents NHCOR<sup>18</sup>, reacting a corresponding compound of formula (I) in which Y represents NH<sub>2</sub> with a compound of general formula (XII), R<sup>18</sup>COCl, wherein R<sup>18</sup> is as hereinbefore defined;

(n) when X represents S and Y represents an optionally substituted aryl or heteroaryl group, reacting a compound of formula (VI) as hereinbefore defined with a compound of general formula



wherein Y' represents an optionally substituted aryl or heteroaryl group and p and A are as hereinbefore defined; or

(p) when X represents S, A represents a C<sub>1-6</sub> alkylene group and Y represents a tetrazolyl group, reacting a compound of formula (I) in which X represents S, A

represents a C<sub>1-6</sub> alkylene group and Y represents CN, with trialkyltin azide (e.g. trimethyltin azide), typically in a solvent such as toluene under reflux conditions; and optionally forming a pharmaceutically acceptable derivative thereof.

Compounds of formula (II) wherein Y represents OH may be prepared by reaction of a compound of formula (VI) as hereinbefore defined with a compound of general formula



10 wherein L'' is a suitable leaving group, for example paratoluenesulphonate, A is as hereinbefore defined, and R<sup>22</sup> is H or a suitable protecting group such as tert-butyldimethylsilyl, in the presence of a suitable base, for example lithium diisopropylamide, in a suitable solvent, for example tetrahydrofuran at around -70° C.

Compounds of formula (II), wherein Y represents OR<sup>11</sup>, CO<sub>2</sub>R<sup>12</sup>, CONR<sup>13</sup>R<sup>14</sup>, NHSO<sub>2</sub>R<sup>17</sup> or NHCOR<sup>18</sup> and wherein R<sup>11</sup> or R<sup>12</sup> as appropriate represent C<sub>1-5</sub> alkyl and R<sup>13</sup> and R<sup>14</sup> or R<sup>17</sup> or R<sup>18</sup> as appropriate are as hereinbefore defined, may be prepared from corresponding compounds of formula (II) wherein Y represent OH, CO<sub>2</sub>H or NH<sub>2</sub> as appropriate in accordance with the methods described in steps (b) to (d), (l) and (m) hereinbefore.

Compounds of formula (VI) are known from *J. Med. Chem.* (1995) 38, 2557, or may be prepared analogously by methods described therein.

Compounds of formula (VII) may be prepared from compounds of formula (II) where Y represents OH by techniques known to those skilled in the art.

30 Compounds of formula (IX) may be prepared by reacting a compound of formula (VI) with lithium diisopropylamide at -78° C., followed by the addition of a halogen.

Other compounds of formula (II), (III), (IV), (V), (VII), (X), (XI), (XII), (XIII) and (XIV) are either commercially available, are well known in the literature or may be prepared easily using known techniques.

40 It will be appreciated by those skilled in the art that in the processes described above the functional groups (e.g. hydroxy or amino groups) of intermediate compounds may need to be protected by protecting groups. The final stage in the preparation of the compounds of formula (I) may involve the removal of one or more protecting groups.

The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', 45 edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T. W. Greene & P. G. M. Wuts, Wiley-Interscience (1991).

Pharmaceutically acceptable derivatives of the compounds of formula (I) include solvates and salts.

50 Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or derivative thereof, with one or more equivalents of the appropriate base or acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. ethanol, tetrahydrofuran or diethyl ether, which may be removed in vacuo, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

Particular salts which may be mentioned include sodium, potassium, hydrochloride, hydrobromide, sulphonate, tosylate and methanesulphonate.

60 The compounds of formula (I) may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

The compounds of formula (I) have a number of chiral centres and may exist in a variety of stereoisomers. The invention provides all optical and stereoisomers, as well as racemic mixtures. The isomers may be resolved or separated by conventional techniques, e.g. chromatography or fractional crystallisation. Enantiomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. chiral HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC, chromatography over silica) or may be made with achiral starting materials and chiral reagents. All stereoisomers are included within the scope of the invention.

The compounds of formula (I) may be isolated from their reaction mixtures using conventional techniques.

The compounds of formula (I) are useful because they possess pharmacological activity in human and non-human animals. They are therefore indicated as pharmaceuticals. In particular they are useful because they possess immunosuppressive activity, for example as demonstrated in the test described below.

The compounds are thus indicated for use in the treatment or prevention of resistance to transplanted organs or tissues, such as kidney, heart, lung, bone marrow, skin and cornea; and of autoimmune, inflammatory, proliferative and hyperproliferative diseases including cancer, and of cutaneous manifestations of immunologically-mediated diseases: for example rheumatoid arthritis, lupus erythematosus, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type 1 diabetes, uveitis, nephrotic syndrome, psoriasis, atopic dermatitis, contact dermatitis and further eczematous dermatitides, seborrhoeic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Alopecia areata, eosinophilic fasciitis and atherosclerosis.

The compounds of formula (I) are also indicated in the treatment of respiratory diseases, for example sarcoidosis, farmer's lung and related diseases, fibroid lung, idiopathic interstitial pneumonia and reversible obstructive airways diseases which latter includes conditions such as asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma), particularly chronic or inveterate asthma (e.g. late asthma and airway hyperresponsiveness) and bronchitis.

Further, the compounds of formula (I) are indicated in the treatment of a disease selected from intestinal inflammations/allergies such as Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease and ulcerative colitis; and food related allergic diseases which have symptomatic manifestation remote from the gastrointestinal tract, for example, migraine, rhinitis and eczema.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disease indicated.

The compounds of formula (I) and pharmaceutically acceptable derivatives thereof, may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the compound or derivative (active ingredient) is in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. The pharmaceutical composition will preferably comprise from 0.05 to 80% w

(per cent by weight), more preferably from 0.10 to 50% w, of active ingredient, and, from 20 to 99.95% w, more preferably from 50 to 99.90% w, of a pharmaceutically acceptable adjuvant, diluent or carrier.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition according to the invention which comprises admixing a compound of formula (I), or a pharmaceutically acceptable derivative thereof, with a pharmaceutically acceptable adjuvant, diluent or carrier.

According to a further aspect of the invention, there is provided a method of effecting immunosuppression which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, to a patient.

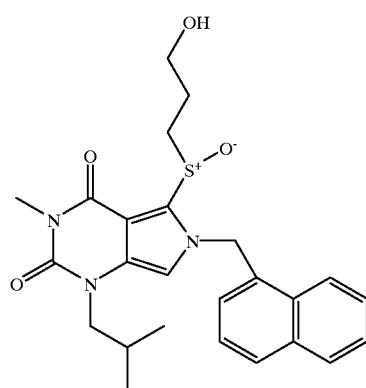
The invention also provides a method of treating, or reducing the risk of, a reversible obstructive airways disease in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

The invention will be further illustrated by reference to the following examples in which MS and NMR are the abbreviations for Mass Spectrometry and Nuclear Magnetic Resonance respectively.

#### EXAMPLE 1

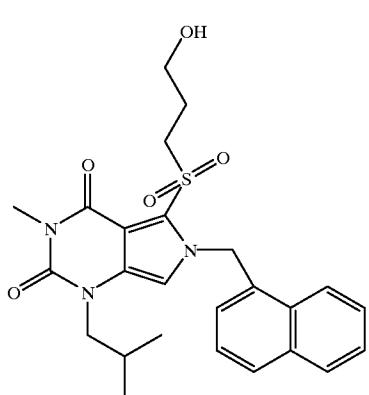
5-[(3-Hydroxypropyl)sulphinyl]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (1) and 5-[(3-hydroxypropyl)sulphonyl]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)dione (2)

(1)



## 11

-continued



To a stirred solution of 5-[(3-hydroxypropyl)thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4-dione (0.39 g; 0.864 mmol; *J. Med. Chem.* (1995) 38, 2557) in dichloromethane (20 ml) was added 3-chloroperoxybenzoic acid (55–60%; 0.526 g). After 30 minutes the reaction was diluted with dichloromethane (80 ml) and washed with sodium bicarbonate solution (50 ml) containing sodium metabisulphite (1 g). The organic layer was dried over magnesium sulphate ( $\text{MgSO}_4$ ), concentrated in vacuo and chromatographed on silica eluting with hexane:acetone (3:2) to give separately the two title compounds which were each subsequently recrystallised from hexane:ethyl acetate [1:2].

## Title Compound 1

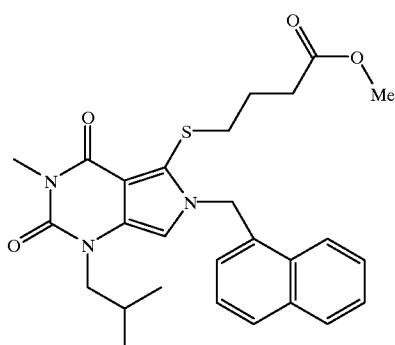
Melting point: 204–206° C. Elemental Analysis (in %): Theory: C 64.22, H 6.25, N 8.99, S 6.86 Found: C 64.10, H 6.51, N 9.22, S 6.53 MS(FAB) 468 ( $\text{M}+\text{H}$ )<sup>+</sup>

## Title Compound 2

Melting point: 201–202° C. Elemental Analysis (in %): Theory: C 62.09, H 6.04, N 8.69, S 6.63 Found: C 61.84, H 6.21, N 8.62, S 6.22 MS(FAB) 484 ( $\text{M}+\text{H}$ )<sup>+</sup>

## EXAMPLE 2

Methyl 4-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoate



## a) 4,4,4-Trimethoxybutyl para-toluenethiosulphonate

A mixture of para-toluenethiosulphonic acid potassium salt (24 mmol), trimethyl 4-bromoorthobutyrate (22 mmol) and hexamethylphosphoramide (30 ml) was stirred at room temperature for 48 h before being poured into 10:1 hexane/diethyl ether (500 ml) and shaken vigorously. The mixture

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was washed with water (2×200 ml) and then brine. The organic phase was collected and dried over magnesium sulphate ( $\text{MgSO}_4$ ) and evaporated to dryness in vacuo to yield the sub-title ester as an oil (5.3 g) containing ca 7% 4,4,4-trimethoxybutylparatoluene(dithioperoxy)sulphonate.

<sup>1</sup>H NMR ( $\text{CDCl}_3$ ) $\delta$  1.95 (2H, m), 2.37 (2H, t), 2.44 (3H, s), 3.02 (2H, t), 3.16 (9H, s), 7.33 (2H, d), 7.80 (2H, d)

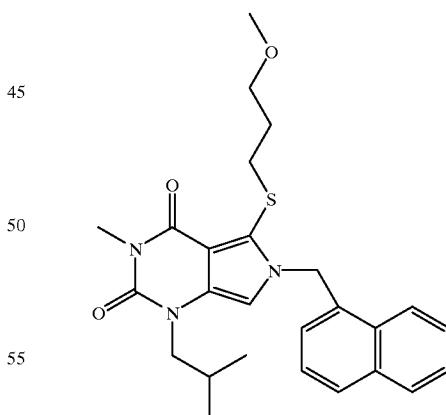
b) Methyl 4-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoate

To a solution of 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H, 6H)-dione (1.4 mmol) in tetrahydrofuran (4 ml) at -78° C. under nitrogen was added a freshly prepared 1M solution of lithium diisopropylamide (8.5 mmol) in tetrahydrofuran followed by 4,4,4-trimethoxybutyl para-toluenethiosulphonate (2.3 mmol). The reaction was allowed to warm to room temperature and then quenched via addition of saturated aqueous  $\text{NH}_4\text{Cl}$  and then brine. The mixture was extracted into diethyl ether which was collected, dried over magnesium sulphate ( $\text{MgSO}_4$ ) and evaporated to dryness in vacuo. The residual oil was redissolved in methanol/water and treated with glacial acetic acid for 0.5 h. The reaction was then basified via addition of solid sodium hydrogencarbonate. The mixture was extracted into diethyl ether, washed with brine, dried over magnesium sulphate ( $\text{MgSO}_4$ ) and evaporated to dryness in vacuo. The resultant oil was chromatographed twice (silica) eluting with 1:3 hexanes/diethyl ether to yield the title compound as an oil (133 mg).

MS (APCI+ve) 464 ( $\text{M}+\text{H}$ )<sup>+</sup> <sup>1</sup>H NMR ( $\text{CDCl}_3$ ) $\delta$  0.88 (6H, d), 1.85 (2H, m), 2.12 (1H, m), 2.40 (2H, m), 3.04 (2H, m), 3.42 (3H, s), 3.55 (2H, d), 3.62 (3H, s), 5.84 (2H, s), 6.35 (1H, s), 6.80 (1H, d), 7.39 (1H, t), 7.57 (2H, m), 7.82 (1H, d), 7.91 (2H, m)

## EXAMPLE 3

5-[(3-Methoxypropyl)thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



To a 60% dispersion of sodium hydride in mineral oil (0.035 g, 0.886 mmol) under nitrogen, was added a solution of 5-[(3-hydroxypropyl)thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (0.20 g) in anhydrous tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 30 minutes, iodomethane (0.055 ml) was added, and stirring was continued for 18 hours. The mixture was added to

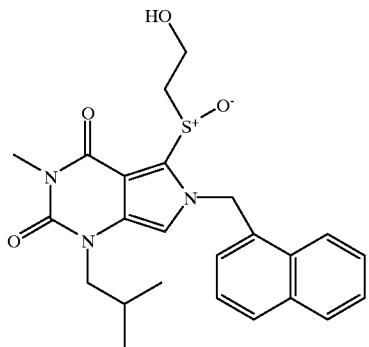
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saturated sodium bicarbonate solution (20 ml) and extracted with ethyl acetate (20 ml). The organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography over silica eluting with hexane:acetone (4:1), and then by column chromatography over silica, eluting with hexane:ethyl acetate (2:1). The resulting oil was crystallised from an ethyl acetate/hexane mixture to give the title compound (95 mg).

Melting point: 92–94° C. MS (FAB) 466 (M+H)<sup>+</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.87 (6H, d), 1.81 (2H, quin), 2.12 (1H, m), 3.07 (2H, t), 3.25 (3H, s), 3.38 (2H, t), 3.43 (3H, s), 3.54 (2H, d), 5.84 (2H, s), 6.34 (1H, s), 6.82 (1H, d), 7.39 (1H, t), 7.53–7.59 (2H, m), 7.83 (1H, d), 7.91–7.93 (2H, m)

## EXAMPLE 4

5-[(2-Hydroxyethyl)sulphinyll]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)dione



## a) Bis-[dimethyl(1,1-dimethylsilyloxyethyl)]disulphide

To a stirred solution of 2-hydroxyethyl disulphide (2 g) and imidazole (5.3 g) in dichloromethane (100 ml) was added dimethyl(1,1-dimethylsilyloxyethyl)silyl chloride. The solution was stirred overnight and then diluted with diethyl ether. The mixture was washed with dilute hydrochloric acid, then with sodium bicarbonate solution and then dried over magnesium sulphate. Concentration in vacuo followed by chromatography on silica gel (hexane:diethyl ether/20:1) gave the subtitle compound as a clear oil (3.75 g). MS (EI) 382 ((M-CH<sub>3</sub>)<sup>+</sup>).

## b) 5-(2-Hydroxyethyl)thio-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

To a stirred solution of 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-pyrrolo[3,4-d]pyrimidine-4,6-dione (J. Med. Chem., 1995, 38, 2557; 0.50 g) and bis-[dimethyl(1,1-dimethylsilyloxyethyl)] disulphide (1.06 g) in anhydrous tetrahydrofuran (15 ml) at -78° C. was added dropwise a solution of lithium diisopropylamide (2.78 mmol) in tetrahydrofuran (5 ml). The solution was stirred for a further 0.5 h at -78° C. and then allowed to warm to ambient temperature. Saturated aqueous sodium bicarbonate solution (10 ml) was added and the solution was extracted with ethyl acetate. The organic extracts were dried over magnesium sulphate and concentrated in vacuo. The residue was redissolved in acetonitrile (10 ml) and treated with 40% aqueous hydrofluoric acid at ambient temperature. The solution was stirred for 1 hour, then neutralised with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic extracts were dried over magnesium sulphate and concentrated in vacuo. Chromatography on

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silica gel (diethyl ether) gave the subtitle compound (0.47 g) as a white solid.

Melting point: 138–141° C. MS (FAB) 353 ((M+H)<sup>+</sup>).

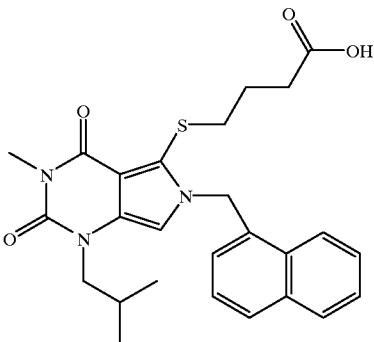
c) 5-[(2-Hydroxyethyl)sulphinyll]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

To a stirred solution of 5-(2-hydroxyethyl)thio-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (100 mg) in methanol (20 ml) was added potassium peroxyomonosulphate (commercially sold under the trade mark "OXONE") (300 mg) in water (10 ml). After stirring for 10 minutes the reaction mixture was diluted with water and extracted with ethyl acetate. The organic extracts were dried over magnesium sulphate and concentrated in vacuo. Chromatography on silica gel (ethyl acetate) gave the title compound (70 mg) as a white foam.

MS (FAB) 454 ((M+H)<sup>+</sup>). <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.85 (3H, d), 0.87 (3H, d), 2.05–2.13 (1H, m), 3.21–3.33 (1H, m), 3.36 (3H, s), 3.49–3.61 (2H, m), 3.65–3.73 (1H, m), 3.84–4.05 (2H, m), 6.17–6.27 (2H, m), 6.42 (1H, s), 6.95 (1H, d), 7.44 (1H, t), 7.54–7.66 (2H, m) and 7.87–7.98 (3H, m).

## EXAMPLE 5

4-[(2,3,4,6-Tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoic acid



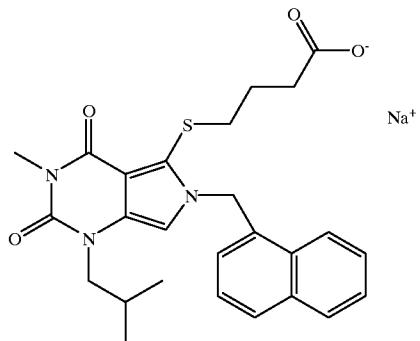
The compound of Example 2, methyl 4-[(2,3,4,6-Tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoate (400 mg), was dissolved in 3:1:1 tetrahydrofuran/methanol/1M lithium hydroxide and stirred for 1.5 h before being acidified by dropwise addition of concentrated hydrochloric acid (HCl). The mixture was then extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulphate (MgSO<sub>4</sub>) and evaporated to dryness in vacuo. The resultant yellow oil was chromatographed (silica), eluting with 200:10:1 dichloromethane/methanol/glacial acetic acid. The resultant red oil was dissolved in toluene and then evaporated, then similarly with trichloromethane to yield a pink foam. The foam was recrystallised from ethyl acetate/hexane to yield 129 mg of the title compound.

MS (APCI+ve) (M+H)<sup>+</sup> 480 Elemental Analysis (in %): Theory: C 65.11, H 6.10, N 8.76, S 6.69 Found: C 65.15, H 6.24, N 8.83, S 6.70 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.88 (6H, d), 1.85 (2H, quin), 2.10 (1H, m), 2.47 (2H, t), 3.02 (2H, t), 3.42 (3H, s), 3.55 (2H, d), 5.84 (2H, s), 6.37 (1H, s), 6.79 (1H, d), 7.38 (1H, t), 7.56 (2H, m), 7.82 (1H, d), 7.91 (2H, m)

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## EXAMPLE 6

4-[(2,3,4,6-Tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoic acid, sodium salt

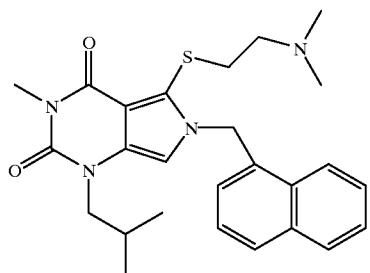


The compound of Example 5,4-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoic acid (200 mg), was dissolved in dioxane (5 ml) and sodium hydroxide solution (2.5 M) (0.163 ml) was added. The solvent was removed by evaporation and freeze drying to give the title compound as a 1:1 mixture with sodium carbonate.

Elemental Analysis for  $C_{27}H_{28}N_3Na_3O_7S$  (in %): Theory: C 53.37, H 4.65, N 6.92, S 5.28 Found: C 53.51, H 5.15, N 6.65, S 5.07 Melting point:>163° C. slow melt MS (APCI) 480 (M+H)<sup>+</sup> <sup>1</sup>H NMR (DMSO)  $\delta$  0.85 (6H,d), 1.4–1.6 (2H,m), 1.80 (2H,t), 2.0–2.2 (1H,m), 2.88 (2H,t), 3.57 (2H,d), 5.89 (2H,s), 6.57 (1H,d), 7.12 (1H,s), 7.41 (1H,t), 7.5–7.7 (2H,m), 7.86 (1H,d), 7.99 (1H,d), 8.18 (1H,d)

## EXAMPLE 7

5-[2-Dimethylaminoethyl]thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



3-Methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (J. Med. Chem., 1995, 38, 2557) (473 mg) and bis(2-dimethylaminoethyl)disulphide (0.6 ml) were dissolved in tetrahydrofuran (10 ml) and cooled to -78° C. Lithium diisopropylamide in tetrahydrofuran (2.5 eq) was added dropwise and the resultant deep red solution was stirred for 75 minutes at -78° C. The cooling bath was removed and the solution allowed to stir for a further 60 minutes. Sodium

## 16

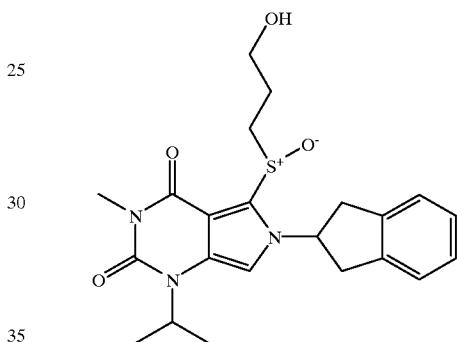
bicarbonate (aqueous) was added followed by ether and the phases were separated. The aqueous phase was extracted twice with ether. The organic phases were combined and washed twice with brine before being dried, filtered and concentrated. The resultant oil was purified by column chromatography (eluant, dichloromethane:methanol:triethylamine 450:50:0.2) and then recrystallised from ether-isohexane to give the title compound (230 mg).

10 Melting point: 140–144° C. MS (APCI+ve) 465 (M+H)<sup>+</sup> <sup>1</sup>H NMR (DMSO)  $\delta$  0.87 (6H, d), 2.01 (6H, s), 2.10–2.16 (1H, m), 2.25 (1H, t), 2.99 (2H, t), 3.25 (3H, s), 3.59 (2H, d), 5.92 (2H, s), 6.54 (1H, d), 7.18 (1H, s), 7.41 (1H, t), 7.58–7.67 (2H, m), 7.86 (1H, d), 7.99 (1H, d), 8.17 (1H, d)

15

## EXAMPLE 8

20 6-(2,3-Dihydro-1H-inden-2-yl)-5-[(3-hydroxypropyl)sulphinyl]-3-methyl-1-(1-methylethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



30 a) 6-(2,3-Dihydro-1H-inden-2-yl)-3-methyl-1-(1-methylethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

40 3,6-Dimethyl-5-formyl-1-(1-methylethyl)pyrimidine-2,4-dione (J. Med. Chem., 1995, 38, 2557; 1.70 g) was dissolved in chloroform (25 ml) and the solution was heated to 50° C. A solution of bromine (0.413 ml) in chloroform (20 ml) was

45 added dropwise to the aldehyde solution over 24 minutes. The reaction was maintained at 50° C. for a further 15 minutes, then allowed to cool to ambient temperature. The reaction mixture was diluted with dichloromethane and was washed successively with water, dilute sodium thiosulphate solution (twice) and brine. The resultant solution was dried, filtered and evaporated to a crude oil which was dissolved in ethanol (50 ml). Triethylamine (3.38 ml) was added to the solution followed by 2-aminoindane (1.49 g) and the mixture was stirred under nitrogen overnight. The reaction

50 mixture was filtered, the white solid collected was washed with a little ethanol and the filtrate was evaporated to give a brown oil. Ethyl acetate was added to the oil and the resultant precipitate was collected by filtration and was

55 washed with a little ethyl acetate. The filtrate was washed with hydrochloric acid (HCl) (2.5 M) and then brine. The resultant ethyl acetate phase was dried, filtered and evaporated to an oil. The oil was purified by chromatography, eluting with isohexane:acetone (4:1) to give a solid which was triturated with hot ethyl acetate:isohexane (3:1) to give the subtitle compound (0.50 g).

60

65

**17**Melting point: 158–160° C. MS (APCI+ve) 3.24 (M+H)<sup>+</sup>

b) 6-(2,3-Dihydro-1H-inden-2-yl)-5-[(3-hydroxypropyl)thio]-3-methyl-1-(1-methylethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

6-(2,3-Dihydro-1H-inden-2-yl)-3-methyl-1-(1-methylethyl)-1H-pyrrolo-[3,4-d]pyrimidine-2,4(3H,6H)-dione (165 mg) and S-{3-[1,1-dimethylethyl]dimethylsilyl}oxypropyl toluenethiosulphonate (J. Med. Chem., 1995, 38, 2557) (362 mg) were dissolved in tetrahydrofuran (6 ml) and the resulting solution was cooled to -78° C. Lithium diisopropylamide in tetrahydrofuran (3 eq) was added dropwise to the cold solution and the resulting solution was stirred for 75 minutes at -78° C. and then the cooling bath was removed. The solution was stirred for a further 75 minutes and then sodium bicarbonate (aqueous) was added. The reaction mixture was extracted thrice with ether. The organic phases were combined and washed twice with brine before being dried, filtered and evaporated. The resultant oil was purified by column chromatography (eluant, isohexane:ethyl acetate 7:2).

The product was dissolved in acetonitrile (10 ml) and hydrofluoric acid (40%, 6 drops) was added. The solution was stirred at ambient temperature for 30 minutes then sodium bicarbonate (aqueous) was added. Ether-ethyl acetate mixture (ca 1:1) was added to the reaction mixture and the phases were separated. The aqueous phase was extracted twice with ether-ethyl acetate mixtures. The organic phases were combined and washed twice with brine before being dried, filtered and concentrated. Crystallisation from ether-cyclohexane gave the subtitle compound (141 mg).

Melting point: 123–125° C. MS (APCI+ve) 414 (M+H)<sup>+</sup>

c) 6-(2,3-Dihydro-1H-inden-2-yl)-5-[(3-hydroxypropyl)sulphiny]-3-methyl-1-(1-methylethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

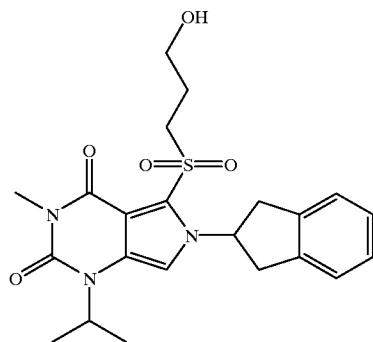
6-(2,3-Dihydro-1H-inden-2-yl)-5-[(3-hydroxypropyl)thio]-3-methyl-1-(1-methylethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (100 mg) was dissolved in methanol (40 ml). Water (10 ml) and potassium peroxy-monosulphate (commercially sold under the trade mark "OXONE") (185 mg) were added and the solution was stirred for 15 minutes. The reaction mixture was diluted with water and then extracted with ethyl acetate thrice. The extracts were combined, washed with brine, then dried, filtered and the solvent was evaporated. The resultant oil was triturated with isohexane, then recrystallised from ethyl acetate-isohexane mixtures to give the title compound (15 mg).

Melting point: 164–165° C. MS (APCI+ve) 430 (M+H)<sup>+</sup>  
<sup>1</sup>H (DMSO d6) δ 1.35 (6H, d), 1.73 (2H, quin), 3.19 (3H, s), 3.26–3.56 (8H, m), 4.65 (1H, t), 4.71 (1H, sept), 6.08–6.12 (1H, m), 7.22–7.32 (4H, m), 7.50 (1H, s)

**18**

EXAMPLE 9

6-(2,3-Dihydro-1H-inden-2-yl)-5-[(3-hydroxypropyl)sulphonyl]-3-methyl-1-(1-methylethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

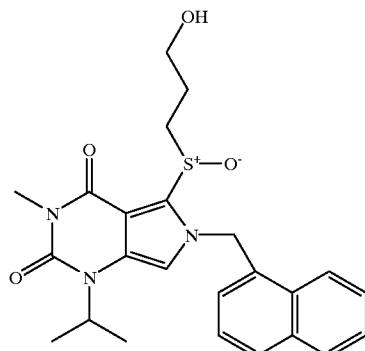


The compound of Example 8, 6-(2,3-Dihydro-1H-inden-2-yl)-5-[(3-hydroxypropyl)sulphonyl]-3-methyl-1-(1-methylethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (80 mg), was dissolved in dichloromethane (5 ml) and 3-chloroperoxybenzoic acid (57–85%) (50 mg) was added. The reaction mixture was stirred for 75 minutes then water and sodium metabisulphite (45 mg) were added and the mixture was stirred for 5 minutes. The phases were separated and the organic phase was washed with sodium bicarbonate (aqueous), then dried, filtered and evaporated. The resultant foam was recrystallised from isohexane-ethyl acetate-ether to give the title compound (15 mg).

Melting point: 171–172° C. MS (APCI+ve) 446 (M+H)<sup>+</sup>  
<sup>1</sup>H NMR (DMSO d6) δ 1.34 (6H, d), 1.73–1.83 (2H, m), 3.22 (3H, s), 3.39–3.50 (6H, m), 3.77–3.83 (2H, m), 4.66 (1H, t), 4.64–4.72 (1H, m), 6.24 (1H, quin), 7.22–7.32 (4H, m), 7.54 (1H, s)

EXAMPLE 10

5-[(3-Hydroxypropyl)sulphiny]-3-methyl-1-(1-methylethyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



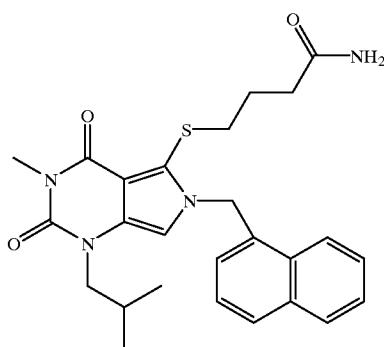
## 19

The title compound was prepared from 5-[(3-Hydroxypropyl)thio]-3-methyl-1-(1-methylethyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H, 6H)-dione (J. Med. Chem., 1995, 38, 2557) in a manner analogous to the method of Example 8 (c) above.

Melting point: 184–185° C. MS (APCI+ve) ( $M+H$ )<sup>+</sup> <sup>1</sup>H NMR ( $CDCl_3$ ) δ 1.35 (3H, d), 1.37 (3H, d), 1.97–2.07 (2H, m), 2.60 (1H, t), 3.24–3.51 (2H, m), 3.72–3.86 (2H, m), 4.68–4.70 (1H, m), 6.23 (2H, s), 6.48 (1H, s), 7.00 (1H, d), 7.44 (1H, t), 7.53–7.62 (2H, m), 7.86–7.94 (2H, m), 7.99–8.02 (1H, m)

## EXAMPLE 11

4-[(2,3,4,6-Tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanamide



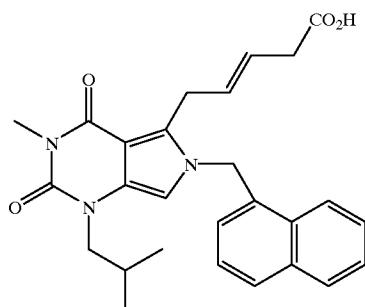
The compound of Example 5,4-[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanoic acid (100 mg), was dissolved in tetrahydrofuran (3 ml) and the solution was cooled in ice. Triethylamine (30  $\mu$ l) was added followed by ethyl chloroformate (21  $\mu$ l); the ice bath was removed and the solution was allowed to stir for 15 minutes and was then cooled in ice again. Aqueous ammonia (0.88 specific gravity, 1 ml) was added and the mixture was stirred for 3 days. The mixture was poured onto water and extracted thrice with dichloromethane. The organic extracts were combined, washed with brine, dried, filtered and evaporated to give an oil which was purified by chromatography, eluting first with ethyl acetate:isohexane:acetic acid (75:25:1) and then with ethyl acetate:acetic acid (199:1) to give the title compound (70 mg).

Melting point: 162–165° C. MS (APCI+ve) 479 ( $M+H$ )<sup>+</sup> <sup>1</sup>H NMR ( $CDCl_3$ ) δ 0.94 (6H, d), 1.86 (2H, quin), 2.12–2.16 (1H, m), 2.45 (2H, t), 2.90 (2H, t), 3.41 (3H, t), 3.56 (2H, d), 5.30 (1H, br), 5.86 (2H, s), 6.08 (1H, br), 6.39 (1H, s), 6.81 (1H, d), 7.40 (1H, dd), 7.58 (2H, m), 7.84 (1H, d), 7.91 (2H, m)

## 20

## EXAMPLE 12

5-(2,3,4,6-Tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)pent-3-enoic acid



a) 5-Iodo-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H, 6H)-dione  
 3-Methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H, 6H)-dione (J. Med. Chem., 1995, 38, 2557; 500 mg) was dissolved in tetrahydrofuran (15 ml) and cooled to –78° C. A solution of lithium diisopropylamide (2 eq) in tetrahydrofuran (5 ml) was added dropwise with stirring at –78° C. Iodine (350 mg) was added and the reaction mixture was allowed to stir at –78° C. for 1 hour and was then allowed to warm to room temperature. The mixture was then poured into saturated ammonium chloride solution and extracted twice with ethyl acetate. The combined organic phases were washed with sodium thiosulphate solution, and with brine, before being dried and evaporated. The resultant foam was chromatographed using isohexane:diethyl ether (1:3) to give a foam which was recrystallised from diethyl ether/isoctane to give the subtitle compound as a pale yellow solid (350 mg).

Melting point: 140–142° C. MS (APCI+ve) 488 ( $M+H$ )<sup>+</sup> <sup>1</sup>H NMR ( $CDCl_3$ ) δ 0.85 (d, 6H), 2.09 (m, 1H), 3.41 (s, 3H), 3.53 (d, 2H), 5.65 (s, 2H), 6.51 (s, 1H), 6.85 (d, 1H), 7.42 (dd, 1H), 7.58 (m, 2H), 7.84–7.95 (m, 3H)

b) Trans-5-(2,3,4,6-Tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)pent-3-enoic acid

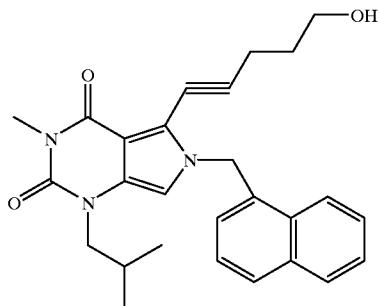
5-Iodo-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H, 6H)-dione (100 mg), 4-pentenoic acid (0.042 ml), palladium acetate (5 mg) and tri(o-tolyl)phosphine (13 mg) were dissolved in triethylamine (1 ml) and acetonitrile (5 ml) and heated to 95° C. in a sealed pressure tube for 3 hours. The reaction mixture was allowed to cool to room temperature and was then evaporated to leave a residue which was chromatographed using ethyl acetate containing 1% acetic acid to give an oil (160 mg). Recrystallisation from diethyl ether/isoctane gave the title compound as a pale brown solid (48 mg).

Melting point: 176–180° C. MS (APCI+ve) 460 ( $M+H$ )<sup>+</sup> (APCI-ve) 458 ( $M-H$ )<sup>-</sup> <sup>1</sup>H NMR ( $CDCl_3$ ) δ 0.89 (d, 6H), 2.14 (m, 1H), 2.98 (d, 2H), 3.40 (s, 3H), 3.56 (d, 2H), 3.82 (d, 2H), 5.50 (dt, [J=15 Hz, 6 Hz]1H), 5.57 (s, 2H), 5.65 (dt, [J=15 Hz, 7 Hz]1H), 6.17 (s, 1H), 6.69 (d, 1H), 7.39 (m, 1H), 7.55 (m, 2H), 7.80–7.93 (m, 3H)

21

## EXAMPLE 13

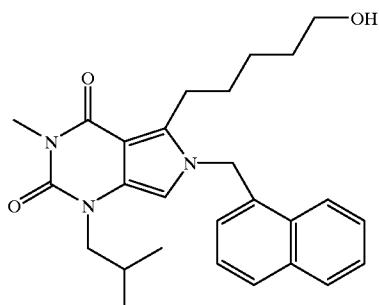
5-(5-Hydroxypent-1-ynyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



5-Iodo-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (100 mg), 4-pentyn-1-ol (0.080 ml), bis-triphenylphosphinepalladium (II) chloride (3 mg) and copper (I) iodide (1 mg) were dissolved in triethylamine (3 ml) and acetonitrile (1 ml) and heated to 90° C. in a sealed pressure tube for 3 hours. The reaction mixture was allowed to cool to room temperature and was then evaporated to leave a residue which was recrystallised from ethyl acetate. The resultant brown solid was chromatographed, eluting with ethyl acetate to give a white solid which was triturated with ethyl acetate to give the title compound (45 mg). Melting point: 176–177° C. MS (APCI+ve) 444 (M+H)<sup>+</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.84 (d, 6H), 1.82 (m, 2H), 2.08 (m, 1H), 2.36 (t, 1H), 2.65 (t, 2H), 3.40 (s, 3H), 3.50 (d, 2H), 3.77 (q, 2H), 5.67 (s, 2H), 6.10 (s, 1H), 7.08 (d, 1H), 7.47 (dd, 1H), 7.55 (m, 2H), 7.86–7.94 (m, 3H)

## EXAMPLE 14

5-(5-Hydroxypentyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



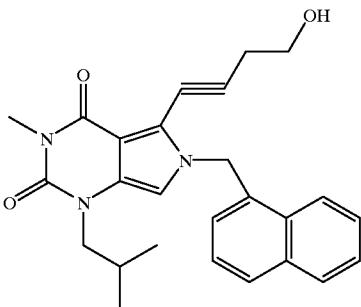
The compound of Example 13, 5-(5-hydroxypent-1-ynyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (75 mg) was suspended in ethanol (50 ml). A suspension of 10% palladium on carbon (7 mg) in ethanol (3 ml) was added and the mixture was hydrogenated. When hydrogen uptake ceased, the reaction mixture was filtered and the solvent was removed by rotary evaporation. The crude product was purified by chromatography on silica eluting with ethyl acetate:isohexane (3:1) to give the title compound (29 mg) as an oil.

22

MS (APCI+ve) 448 (M+H)<sup>+</sup>; (APCI-ve) 446 (M-H)<sup>-</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.90 (6H, d), 1.3–1.65 (6H, m), 2.17 (1H, m), 3.01 (2H, t), 3.41 (3H, s), 3.55–3.58 (4H, m), 3.64 (1H, t), 5.57 (2H, s), 6.70 (1H, d), 7.39 (1H, t), 7.56–7.60 (2H, m), 7.85–7.95 (3H, m)

## EXAMPLE 15

5-(4-Hydroxybut-1-ynyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

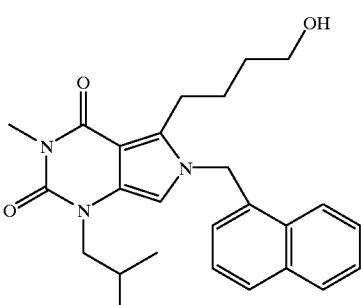


The title compound was prepared from 5-iodo-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione and 3-butyn-1-ol in a manner analogous to the method of Example 13 above.

Melting point: 170–171° C. MS (APCI+ve) 430 (M+H)<sup>+</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.84 (d, 6H), 2.09 (m, 1H), 2.74 (t, 2H), 3.40 (s, 3H), 3.50 (d, 2H), 3.88 (m, 3H), 5.68 (s, 2H), 6.08 (s, 1H), 7.10 (d, 1H), 7.46 (t, 1H), 7.55 (m, 2H), 7.87–7.94 (m, 3H)

## EXAMPLE 16

5-(4-Hydroxybutyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

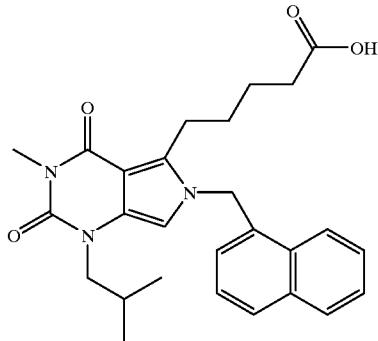


The title compound was prepared from the compound of Example 15, 5-(4-hydroxybut-1-ynyl)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione, in a manner analogous to the method of Example 14 above.

MS (APCI+ve) 434 (M+H)<sup>+</sup>; (APCI-ve) 432 (M-H)<sup>-</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.88 (6H, d), 1.56–1.72 (4H, m), 2.18 (1H, m), 2,3 (1H, br), 3.01 (2H, t), 3.41 (3H, s), 3.57 (2H, d), 3.65–3.70 (2H, m), 5.58 (2H, s), 6.69 (1H, d), 7.41 (1H, t), 7.56–7.62 (2H, m), 7.84 (1H, d), 7.88–7.95 (2H, m)

**23**  
EXAMPLE 17

5-(2,3,4,6-Tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)pentanoic acid



a) 5-(2,3,4,6-Tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)pent-4-ynoic acid

The sub-title compound was prepared from 5-iodo-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione, and 4-pentyneoic acid in the presence of bistrimethylsilyltrifluoroacetamide in a manner analogous to the method of Example 13 above.

MS (APCI+ve) 458 (M+H)<sup>+</sup>, (APCI-ve) 456 (M-H)<sup>-</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.85 (d, 6H), 2.07 (m, 1H), 2.61 (m, 2H), 2.80 (t, 2H), 3.39 (s, 3H), 3.48 (d, 2H), 5.65 (s, 2H), 6.09 (s, 1H), 7.11 (d, 1H), 7.44 (dd, 1H), 7.53 (m, 2H), 7.88–7.94 (m, 3H)

b) 5-(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)pentanoic acid

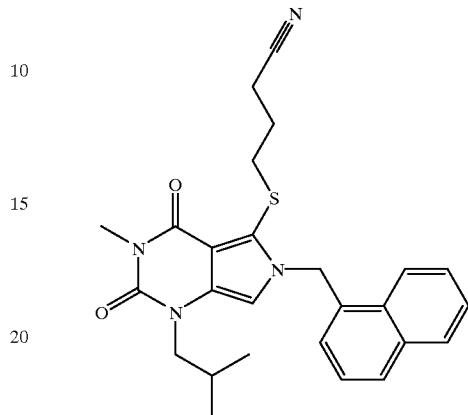
The title compound was prepared from 5-(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)-pent-4-ynoic acid in a manner analogous to the method of Example 14 above.

Melting point: 146–147° C. MS (APCI+ve) 462 (M+H), (APCI-ve) 460 (M-H) <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 0.90 (d, 6H), 1.66 (m, 4H), 2.16 (m, 1H), 2.34 (t, 2H), 3.02 (t, 2H), 3.40 (s, 3H), 3.56 (d, 2H), 5.56 (s, 2H), 6.15 (s, 1H), 6.69 (d, 1H), 7.38 (t, 1H), 7.53–7.62 (m, 2H), 7.82–7.94 (m, 3H)

60 65

**24**  
EXAMPLE 18

4-[(2,3,4,6-Tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4-dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanenitrile



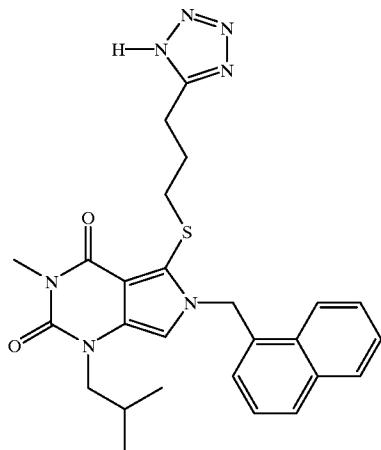
a) 5-[(3-{Methanesulphonyloxy}propyl)thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320 1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380 1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440 1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500 1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560 1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620 1625 1630 1635 1640 1645 1650 1655 1660 1665 1670 1675 1680 1685 1690 1695 1700 1705 1710 1715 1720 1725 1730 1735 1740 1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800 1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860 1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100 2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160 2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220 2225 2230 2235 2240 2245 2250 2255 2260 2265 2270 2275 2280 2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340 2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400 2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460 2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520 2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580 2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640 2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700 2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760 2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820 2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880 2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940 2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000 3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060 3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120 3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180 3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240 3245 3250 3255 3260 3265 3270 3275 3280 3285 3290 3295 3300 3305 3310 3315 3320 3325 3330 3335 3340 3345 3350 3355 3360 3365 3370 3375 3380 3385 3390 3395 3400 3405 3410 3415 3420 3425 3430 3435 3440 3445 3450 3455 3460 3465 3470 3475 3480 3485 3490 3495 3500 3505 3510 3515 3520 3525 3530 3535 3540 3545 3550 3555 3560 3565 3570 3575 3580 3585 3590 3595 3600 3605 3610 3615 3620 3625 3630 3635 3640 3645 3650 3655 3660 3665 3670 3675 3680 3685 3690 3695 3700 3705 3710 3715 3720 3725 3730 3735 3740 3745 3750 3755 3760 3765 3770 3775 3780 3785 3790 3795 3800 3805 3810 3815 3820 3825 3830 3835 3840 3845 3850 3855 3860 3865 3870 3875 3880 3885 3890 3895 3900 3905 3910 3915 3920 3925 3930 3935 3940 3945 3950 3955 3960 3965 3970 3975 3980 3985 3990 3995 4000 4005 4010 4015 4020 4025 4030 4035 4040 4045 4050 4055 4060 4065 4070 4075 4080 4085 4090 4095 4010 4015 4020 4025 4030 4035 4040 4045 4050 4055 4060 4065 4070 4075 4080 4085 4090 4095 4100 4105 4110 4115 4120 4125 4130 4135 4140 4145 4150 4155 4160 4165 4170 4175 4180 4185 4190 4195 4200 4205 4210 4215 4220 4225 4230 4235 4240 4245 4250 4255 4260 4265 4270 4275 4280 4285 4290 4295 4300 4305 4310 4315 4320 4325 4330 4335 4340 4345 4350 4355 4360 4365 4370 4375 4380 4385 4390 4395 4400 4405 4410 4415 4420 4425 4430 4435 4440 4445 4450 4455 4460 4465 4470 4475 4480 4485 4490 4495 4500 4505 4510 4515 4520 4525 4530 4535 4540 4545 4550 4555 4560 4565 4570 4575 4580 4585 4590 4595 4600 4605 4610 4615 4620 4625 4630 4635 4640 4645 4650 4655 4660 4665 4670 4675 4680 4685 4690 4695 4700 4705 4710 4715 4720 4725 4730 4735 4740 4745 4750 4755 4760 4765 4770 4775 4780 4785 4790 4795 4800 4805 4810 4815 4820 4825 4830 4835 4840 4845 4850 4855 4860 4865 4870 4875 4880 4885 4890 4895 4900 4905 4910 4915 4920 4925 4930 4935 4940 4945 4950 4955 4960 4965 4970 4975 4980 4985 4990 4995 5000 5005 5010 5015 5020 5025 5030 5035 5040 5045 5050 5055 5060 5065 5070 5075 5080 5085 5090 5095 5100 5105 5110 5115 5120 5125 5130 5135 5140 5145 5150 5155 5160 5165 5170 5175 5180 5185 5190 5195 5200 5205 5210 5215 5220 5225 5230 5235 5240 5245 5250 5255 5260 5265 5270 5275 5280 5285 5290 5295 5300 5305 5310 5315 5320 5325 5330 5335 5340 5345 5350 5355 5360 5365 5370 5375 5380 5385 5390 5395 5400 5405 5410 5415 5420 5425 5430 5435 5440 5445 5450 5455 5460 5465 5470 5475 5480 5485 5490 5495 5500 5505 5510 5515 5520 5525 5530 5535 5540 5545 5550 5555 5560 5565 5570 5575 5580 5585 5590 5595 5600 5605 5610 5615 5620 5625 5630 5635 5640 5645 5650 5655 5660 5665 5670 5675 5680 5685 5690 5695 5700 5705 5710 5715 5720 5725 5730 5735 5740 5745 5750 5755 5760 5765 5770 5775 5780 5785 5790 5795 5800 5805 5810 5815 5820 5825 5830 5835 5840 5845 5850 5855 5860 5865 5870 5875 5880 5885 5890 5895 5900 5905 5910 5915 5920 5925 5930 5935 5940 5945 5950 5955 5960 5965 5970 5975 5980 5985 5990 5995 6000 6005 6010 6015 6020 6025 6030 6035 6040 6045 6050 6055 6060 6065 6070 6075 6080 6085 6090 6095 6100 6105 6110 6115 6120 6125 6130 6135 6140 6145 6150 6155 6160 6165 6170 6175 6180 6185 6190 6195 6200 6205 6210 6215 6220 6225 6230 6235 6240 6245 6250 6255 6260 6265 6270 6275 6280 6285 6290 6295 6300 6305 6310 6315 6320 6325 6330 6335 6340 6345 6350 6355 6360 6365 6370 6375 6380 6385 6390 6395 6400 6405 6410 6415 6420 6425 6430 6435 6440 6445 6450 6455 6460 6465 6470 6475 6480 6485 6490 6495 6500 6505 6510 6515 6520 6525 6530 6535 6540 6545 6550 6555 6560 6565 6570 6575 6580 6585 6590 6595 6600 6605 6610 6615 6620 6625 6630 6635 6640 6645 6650 6655 6660 6665 6670 6675 6680 6685 6690 6695 6700 6705 6710 6715 6720 6725 6730 6735 6740 6745 6750 6755 6760 6765 6770 6775 6780 6785 6790 6795 6800 6805 6810 6815 6820 6825 6830 6835 6840 6845 6850 6855 6860 6865 6870 6875 6880 6885 6890 6895 6900 6905 6910 6915 6920 6925 6930 6935 6940 6945 6950 6955 6960 6965 6970 6975 6980 6985 6990 6995 7000 7005 7010 7015 7020 7025 7030 7035 7040 7045 7050 7055 7060 7065 7070 7075 7080 7085 7090 7095 7100 7105 7110 7115 7120 7125 7130 7135 7140 7145 7150 7155 7160 7165 7170 7175 7180 7185 7190 7195 7200 7205 7210 7215 7220 7225 7230 7235 7240 7245 7250 7255 7260 7265 7270 7275 7280 7285 7290 7295 7300 7305 7310 7315 7320 7325 7330 7335 7340 7345 7350 7355 7360 7365 7370 7375 7380 7385 7390 7395 7400 7405 7410 7415 7420 7425 7430 7435 7440 7445 7450 7455 7460 7465 7470 7475 7480 7485 7490 7495 7500 7505 7510 7515 7520 7525 7530 7535 7540 7545 7550 7555 7560 7565 7570 7575 7580 7585 7590 7595 7600 7605 7610 7615 7620 7625 7630 7635 7640 7645 7650 7655 7660 7665 7670 7675 7680 7685 7690 7695 7700 7705 7710 7715 7720 7725 7730 7735 7740 7745 7750 7755 7760 7765 7770 7775 7780 7785 7790 7795 7800 7805 7810 7815 7820 7825 7830 7835 7840 7845 7850 7855 7860 7865 7870 7875 7880 7885 7890 7895 7900 7905 7910 7915 7920 7925 7930 7935 7940 7945 7950 7955 7960 7965 7970 7975 7980 7985 7990 7995 8000 8005 8010 8015 8020 8025 8030 8035 8040 8045 8050 8055 8060 8065 8070 8075 8080 8085 8090 8095 8100 8105 8110 8115 8120 8125 8130 8135 8140 8145 8150 8155 8160 8165 8170 8175 8180 8185 8190 8195 8200 8205 8210 8215 8220 8225 8230 8235 8240 8245 8250 8255 8260 8265 8270 8275 8280 8285 8290 8295 8300 8305 8310 8315 8320 8325 8330 8335 8340 8345 8350 8355 8360 8365 8370 8375 8380 8385 8390 8395 8400 8405 8410 8415 8420 8425 8430 8435 8440 8445 8450 8455 8460 8465 8470 8475 8480 8485 8490 8495 8500 8505 8510 8515 8520 8525 8530 8535 8540 8545 8550 8555 8560 8565 8570 8575 8580 8585 8590 8595 8600 8605 8610 8615 8620 8625 8630 8635 8640 8645 8650 8655 8660 8665 8670 8675 8680 8685 8690 8695 8700 8705 8710 8715 8720 8725 8730 8735 8740 8745 8750 8755 8760 8765 8770 8775 8780 8785 8790 8795 8800 8805 8810 8815 8820 8825 8830 8835 8840 8845 8850 8855 8860 8865 8870 8875 8880 8885 8890 8895 8900 8905 8910 8915 8920 8925 8930 8935 8940 8945 8950 8955 8960 8965 8970 8975 8980 8985 8990 8995 9000 9005 9010 9015 9020 9025 9030 9035 9040 9045 9050 9055 9060 9065 9070 9075 9080 9085 9090 9095 9100 9105 9110 9115 9120 9125 9130 9135 9140 9145 9150 9155 9160 9165 9170 9175 9180 9185 9190 9195 9200 9205 9210 9215 9220 9225 9230 9235 9240 9245 9250 9255 9260 9265 9270 9275 9280 9285 9290 9295 9300 9305 9310 9315 9320 9325 9330 9335 9340 9345 9350 9355 9360 9365 9370 9375 9380 9385 9390 9395 9400 9405 9410 9415 9420 9425 9430 9435 9440 9445 9450 9455 9460 9465 9470 9475 9480 9485 9490 9495 9500 9505 9510 9515 9520 9525 9530 9535 9540 9545 9550 9555 9560 9565 9570 9575 9580 9585 9590 9595 9600 9605 9610 9615 9620 9625 9630 9635 9640 9645 9650 9655 9660 9665 9670 9675 9680 9685 9690 9695 9700 9705 9710 9715 9720 9725 9730 9735 9740 9745 9750 9755 9760 9765 9770 9775 9780 9785 9790 9795 9800 9805 9810 9815 9820 9825 9830 9835 9840 984

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EXAMPLE 19

5-[(3-{1H-Tetrazol-5-yl}propyl)thio]-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo-[3,4-d]pyrimidine-2,4(3H,6H)-dione

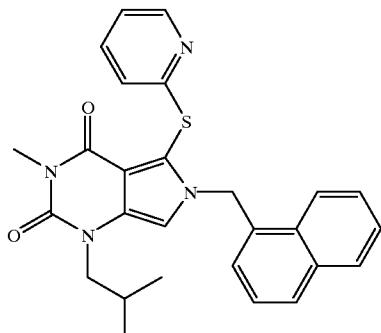


The compound of Example 18, 4[(2,3,4,6-tetrahydro-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-2,4dioxo-1H-pyrrolo[3,4-d]pyrimidin-5-yl)thio]butanenitrile (98 mg) was dissolved in toluene (20 ml) and trimethyltin azide (100 mg) was added. The solution was heated under reflux for 110 hours, then the solvent was evaporated and the residue was chromatographed, eluting with ethanol:dichloromethane (1:19), to give the title compound (30 mg).

MS (+ve APCI) ( $M+H$ )<sup>+</sup> 504 <sup>1</sup>H NMR (DMSO d-6)  $\delta$  0.86 (6H, d), 1.79 (2H, quin), 2.05–2.16 (1H, m), 2.87 (2H, t), 2.91 (2H, t), 3.23 (3H, s), 3.59 (2H, d), 5.90 (2H, s), 6.54 (1H, d), 7.19 (1H, s), 7.38 (1H, t), 7.57–7.66 (2H, m), 7.85 (1H, d), 7.99 (1H, d), 8.17 (1H, d)

EXAMPLE 20

3-Methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-5-[(2-pyridinyl)thio]-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



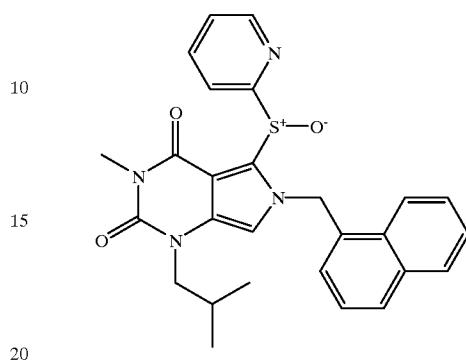
Prepared from 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo-[3,4-d]pyrimidine-2,4(3H,6H)-dione (J. Med. Chem., 1995, 38, 2557) and 2,2'-pyridyl disulphide following the method of Example 7.

Melting point: 146–148° C. MS (FAB) ( $(M+H)^+$ ) 471 <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.85 (6H, d), 2.08 (1H, m), 3.38 (3H, s), 3.52 (2H, d), 5.78 (2H, s), 6.39 (1H, s), 7.03 (1H, m), 7.10 (2H, m), 7.44 (4H, m), 7.86 (3H, m), 8.38 (1H, d)

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EXAMPLE 21

3-Methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-5-[(2-pyridinyl)sulphinyl]-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

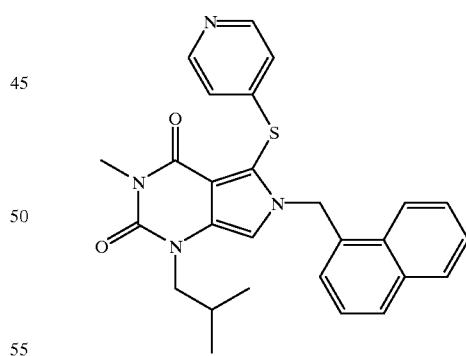


Prepared from the compound of Example 20, 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-5-[(2-pyridinyl)thio]-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione and potassium peroxymonosulphate (commercially sold under the trade mark "OXONE") following the method of Example 8 c).

MS (FAB) ( $(M+H)^+$ ) 487 <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.81 (6H, d), 2.04 (1H, m), 3.43 (3H, s), 3.49 (2H, m), 5.83 (1H, d), 5.94 (1H, d), 6.24 (1H, s), 6.64 (1H, d), 7.07 (1H, m), 7.20 (1H, t), 7.47 (3H, m), 7.70 (2H, m), 7.84 (1H, d), 7.92 (1H, d), 8.48 (1H, d)

EXAMPLE 22

3-Methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-5-[(4-pyridinyl)thio]-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



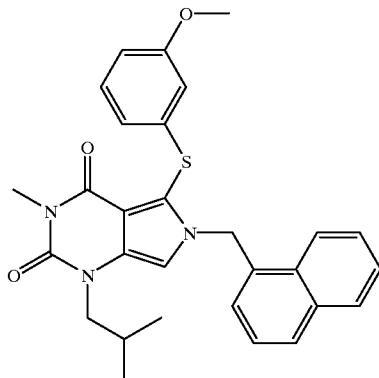
Prepared from 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)1H-pyrrolo-[3,4-d]pyrimidine-2,4(3H,6H)-dione (J. Med. Chem., 1995, 38, 2557) and 4,4'-pyridyl disulphide following the method of Example 7.

Melting point: 154–156° C. MS (FAB) 471 ( $(M+H)^+$ ) <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  0.87 (6H, d), 2.11 (1H, m), 3.38 (3H, s), 3.56 (2H, d), 5.70 (2H, s), 6.51 (1H, s), 6.88 (2H, m), 6.92 (1H, d), 7.35 (1H, t), 7.48 (2H, m), 7.75 (1H, d), 7.81 (1H, d), 7.87 (1H, d), 8.34 (2H, d)

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EXAMPLE 23

5-([3-Methoxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



a) 3-Methoxyphenyldisulphide

4-Toluenesulphonylchloride (8 g) was added portionwise to a solution of 3-methoxythiophenol (5 ml) and triethylamine (5.6 ml) in dichloromethane (50 ml) at 0° C. After 3.5 hours the reaction mixture was diluted with dichloromethane and washed once with water, twice with dilute hydrochloric acid, twice with saturated sodium hydrogen carbonate solution and once with brine. The organic layer was dried over magnesium sulphate, filtered and evaporated in vacuo. Purification of the residue by chromatography on silica gel, eluting with isohexane/ethyl acetate (19:1), gave the subtitle compound as an oil (2.65 g).

MS (EI) ( $M^+$ ) 278  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.77 (6H, s), 6.75 (2H, dd), 7.06 (2H, s), 7.07 (2H, d), 7.21 (2H, t)

b) 5-([3-Methoxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

To a stirred solution of 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (0.50 g) (J. Med. Chem., 1995, 38, 2557) and 3-methoxyphenyldisulphide (0.77 g) in anhydrous tetrahydrofuran (20 ml) at -70° C. was added dropwise a solution of lithium diisopropylamide (2.79 mmol) in tetrahydrofuran (7 ml). The solution was stirred for a further 2 hours at -70° C. and then allowed to warm to ambient temperature. Water (10 ml) was added and the solution was extracted with ethyl acetate. The organic phase was separated and washed once with water, twice with dilute hydrochloric acid, twice with saturated sodium hydrogen carbonate solution and once with brine. The organic layer was dried over magnesium sulphate and evaporated in vacuo. Purification by chromatography on silica gel, eluting with isohexane/ethyl acetate (4:1 to 2:1) followed by recrystallisation from isohexane/ethyl acetate (4:1), gave the title compound (430 mg).

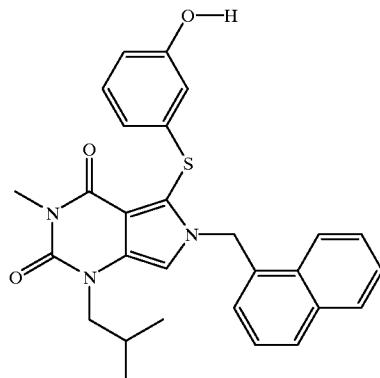
Melting point: 130–133° C. MS (APCI) 500 ( $(M+H)^+$ )  $^1\text{H}$  NMR (DMSO)  $\delta$  0.86 (6H, d), 2.1–2.2 (1H, m), 3.22 (3H, s), 3.60 (3H, s), 3.62 (2H, d), 5.86 (2H, s), 6.55–6.65 (3H, m), 6.73 (1H, dd), 7.16 (1H, t), 7.33 (2H, t), 7.50–7.60 (2H, m), 7.83 (1H, d), 7.96 (1H, dd), 8.05 (1H, dd)

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EXAMPLE 24

5-([3-Hydroxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

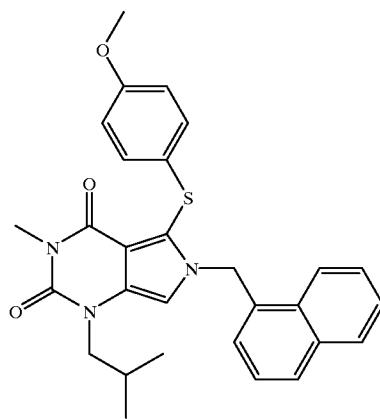


A solution of boron tribromide in dichloromethane (1M, 3 ml) was added to a solution of 5-([3-methoxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (200 mg) (compound of Example 23) in dichloromethane (20 ml) at ambient temperature. After 6 hours, water (10 ml) was added carefully and the reaction mixture was partitioned between dichloromethane and brine. The organic phase was dried over magnesium sulphate, filtered and evaporated in vacuo. Purification by chromatography on silica gel, eluting with isohexane/ethyl acetate (2:1 to 1:1) followed by recrystallisation from isohexane/ethyl acetate (3:1), gave the title compound (120 mg).

Melting point: 150–151° C. MS (APCI) 486 ( $(M+H)^+$ )  $^1\text{H}$  NMR (DMSO)  $\delta$  0.86 (6H, d), 2.1–2.2 (1H, m), 3.23 (3H, s), 3.61 (2H, d), 5.83 (2H, s), 6.45 (1H, t), 6.53 (2H, dt), 6.63 (1H, d), 7.03 (1H, t), 7.30 (1H, s), 7.36 (1H, t), 7.50–7.60 (2H, m), 7.85 (1H, d), 7.96 (1H, dd), 8.05 (1H, dd), 9.51 (1H, brs)

EXAMPLE 25

5-([4-Methoxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



Prepared from 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,

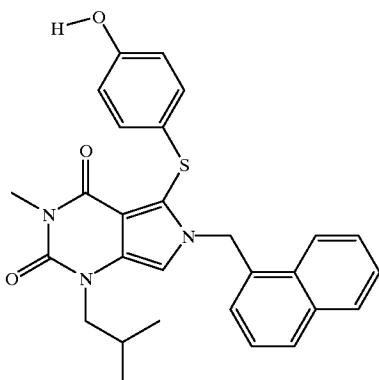
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6H)-dione (0.50 g) (J. Med. Chem., 1995, 38, 2557) and 4-methoxyphenyldisulphide following the method of Example 23.

Melting point: 60–63° C. (foam) MS (APCI) 500 ((M+H)<sup>+</sup>) <sup>1</sup>H NMR (DMSO) δ 0.81 (6H, d), 2.1–2.2 (1H, m), 3.24 (3H, s), 3.58 (2H, d), 3.68 (3H, s), 5.91 (2H, s), 6.50 (1H, d), 6.80 (2H, d), 7.20 (3H, d), 7.31 (1H, t), 7.55–7.60 (2H, m), 7.83 (1H, d), 7.98 (1H, dd), 8.08 (1H, dd)

EXAMPLE 26

5-([4-Hydroxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione

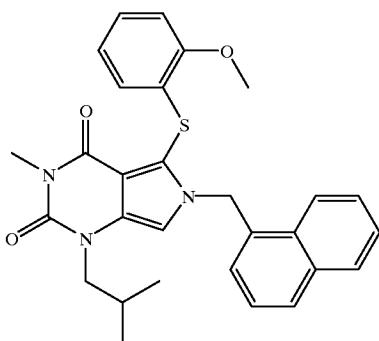


Prepared from the compound of Example 25 following the method of Example 24.

Melting point: 228–230° C. MS (APCI) 486 ((M+H)<sup>+</sup>) <sup>1</sup>H NMR (DMSO) δ 0.83 (6H, d), 2.1–2.2 (1H, m), 3.24 (3H, s), 3.56 (2H, d), 5.91 (2H, s), 6.52 (1H, d), 6.63 (2H, d), 7.14–7.16 (3H, m), 7.35 (1H, t), 7.55–7.60 (2H, m), 7.84 (1H, d), 7.97 (1H, dd), 8.06 (1H, dd), 9.59 (1H, s)

EXAMPLE 27

5-([2-Methoxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



Prepared following the method of Example 23 using 3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione (0.50 g) (J. Med. Chem., 1995, 38, 2557) and 2-methoxyphenyldisulphide.

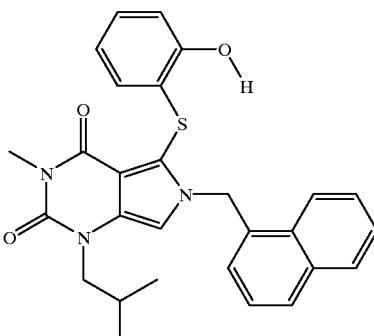
Melting point: 153° C. MS (APCI) 500 ((M+H)<sup>+</sup>) <sup>1</sup>H NMR (DMSO) δ 0.87 (6H, d), 2.1–2.2 (1H, m), 3.21 (3H, s), 3.61

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(2H, d), 3.69 (3H, s), 5.85 (2H, s), 6.59 (1H, d), 6.69 (1H, dd), 6.81 (1H, dt), 6.91 (1H, dd), 7.12 (1H, dt), 7.34 (2H, t), 7.55–7.60 (2H, m), 7.82 (1H, d), 7.96 (1H, dd), 8.05 (1H, dd)

EXAMPLE 28

5-([2-Hydroxyphenyl]thio)-3-methyl-1-(2-methylpropyl)-6-(1-naphthalenylmethyl)-1H-pyrrolo[3,4-d]pyrimidine-2,4(3H,6H)-dione



Prepared from the compound of Example 27 following the method of Example 24.

Melting point: 190–192° C. MS (APCI) 486 ((M+H)<sup>+</sup>) <sup>1</sup>H NMR (DMSO) δ 0.85 (6H, d), 2.1–2.2 (1H, m), 3.22 (3H, s), 3.59 (2H, d), 5.88 (2H, s), 6.63 (1H, d), 6.69 (1H, dd), 6.79 (2H, dt), 7.00 (1H, dt), 7.26 (1H, s), 7.37 (1H, t), 7.55–7.60 (2H, m), 7.85 (1H, d), 7.96 (1H, dd), 8.05 (1H, dd), 10.02 (1H, s)

EXAMPLE 29

Inhibition of Human Mixed Lymphocyte Reaction (MLR)

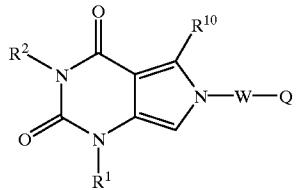
The MLR test was performed in 96-well flat bottomed microtitre plates. Compounds were prepared as 10 mM stock solution in dimethyl sulphoxide. A 50 fold dilution of this was prepared in a cell culture solution obtained from the Roswell Park Memorial Institute (RPMI 1640 medium). Serial dilutions were prepared from this solution. 10  $\mu$ l of the 50 fold diluted stock, or dilutions of it, were added to the wells to give concentrations in the assay starting at 9.5  $\mu$ M and decreasing. Into each well was placed  $1.5 \times 10^5$  cells from each of two responding donors in a final volume of 0.2 ml RPMI 1640 medium supplemented with 10% human serum, 2 mM L-glutamine and penicillin/streptomycin. The cells were incubated at 37° C. in a humidified atmosphere at 5% carbon dioxide for 120 hours. <sup>3</sup>H-Thymidine (0.5  $\mu$ Ci) was added for the final 6 hours of the incubation. The level of radioactivity incorporated by the cells was then determined, which is a measure of T-cell proliferation.

The title compounds of Examples 1 to 28 were found to exhibit an  $IA_{50}$  value of less than  $1 \times 10^{-6}$  M in the above test.

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What is claimed is:

1. A process for the preparation of a compound of formula (I)



(I) 5

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wherein:

W represents  $-\text{CH}_2-$  or a bond; Q represents  $\text{Ar}^1$  or  $\text{Ar}^2$ ;  
 in the case where W represents  $-\text{CH}_2-$ , Q represents  
 an aryl group  $\text{Ar}^1$  wherein  $\text{Ar}^1$  represents naphthyl,  
 phenyl, quinolyl, isoquinolyl, indolyl, benzofuranyl or

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benzothienyl; in the case where W represents a bond, Q represents an aryl group  $\text{Ar}^2$  wherein  $\text{Ar}^2$  represents acenaphthienyl, fluorenyl or indanyl; wherein the ring systems which  $\text{Ar}^1$  and  $\text{Ar}^2$  represent may all be optionally substituted by one or more substituents selected from  $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkoxy, halogen, or trifluoromethyl;  $\text{R}^{10}$  represents  $\text{X}-\text{A}_p-\text{Y}$ ; X represents  $\text{S}(\text{O})_n$ ,  $\text{C}\equiv\text{C}$ ,  $(\text{CH}_2)_2$ ,  $\text{CH}=\text{CH}$  or  $\text{CH}_2\text{CH}=\text{CH}$ ; n represents 0, 1 or 2; A represents  $\text{C}_{1-6}$  alkylene; p is 0 or 1; Y represents  $\text{COOH}$ , provided that when X represents  $\text{S}(\text{O})_n$ , then p is 1; and  $\text{R}^1$  and  $\text{R}^2$  independently represent H or  $\text{C}_{1-5}$  alkyl; which process comprises, hydrolyzing a corresponding  $\text{C}_{1-5}$  alkyl ester compound and optionally converting the compound of formula (I) obtained to a pharmaceutically acceptable salt or solution.

\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 6,211,368 B1

Page 1 of 1

DATED : April 3, 2001

INVENTOR(S) : Cooper, Martin; Cheshire, David; Donald, David; Tomkinson, Nicholas

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1 (colum 32, line 16), the expression "or solution" should read "or solvate thereof."

Signed and Sealed this

Fourth Day of September, 2001

*Attest:*

*Nicholas P. Godici*

Attesting Officer

NICHOLAS P. GODICI  
Acting Director of the United States Patent and Trademark Office